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Chemotherapeutic Agents

PRINCIPAL INVESTIGATOR: Jeffrey D. Winkler, Ph.D.

CONTRACTING ORGANIZATION: University of Pennsylvania
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This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™. The recent discovery of two other natural products, epothilone and eleutherobin, that operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach using synthetic and computational studies for the elucidation of the pharmacophore common to these structurally dissimilar substances. Such an advance could lead to the development of a novel family of prostate cancer chemotherapeutics.

We describe herein our approach to the synthesis of novel analogs of the potent antitumor agent eleutherobin.

Prostate Cancer

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FOREWORD

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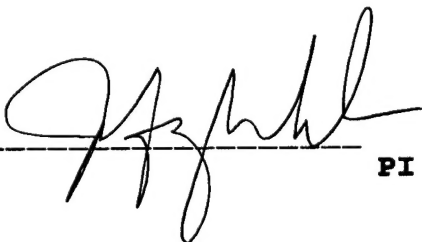
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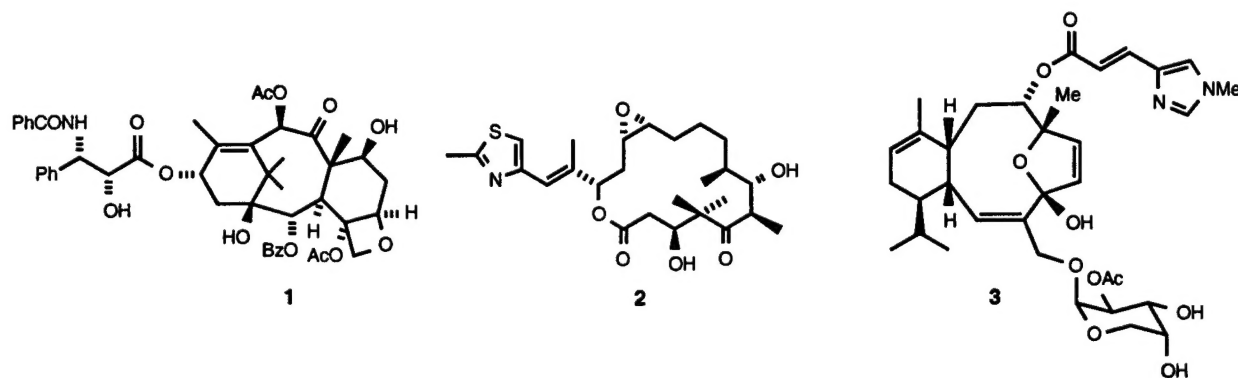
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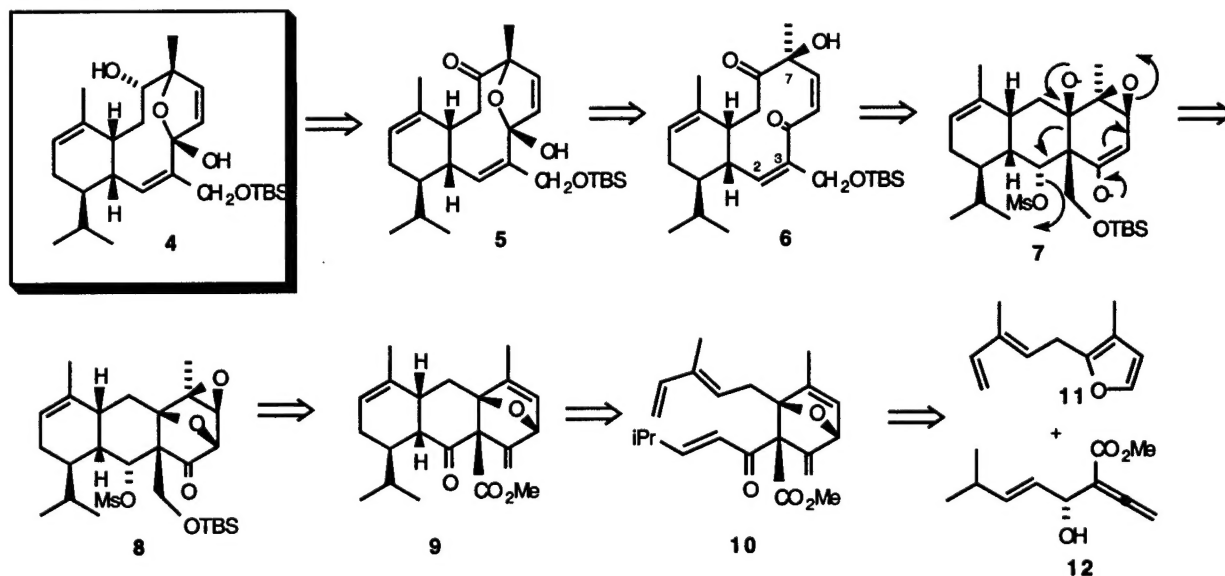
INTRODUCTION

This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™ 1. The recent discovery of two other natural products, epothilone 2, and eleutherobin 3, which operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach to the elucidation of the pharmacophore common to these structurally dissimilar substances, using a combination of synthetic and computational studies. Such an advance could lead to the development of a novel family of prostate cancer chemotherapeutics.



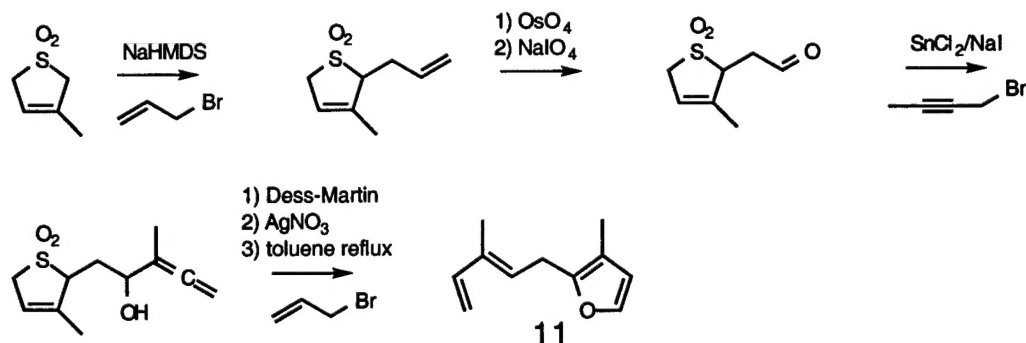
BODY

The recent discovery that eleutherobin is the most biologically potent of the three aforementioned natural product classes has prompted us to pursue the synthesis of eleutherobin

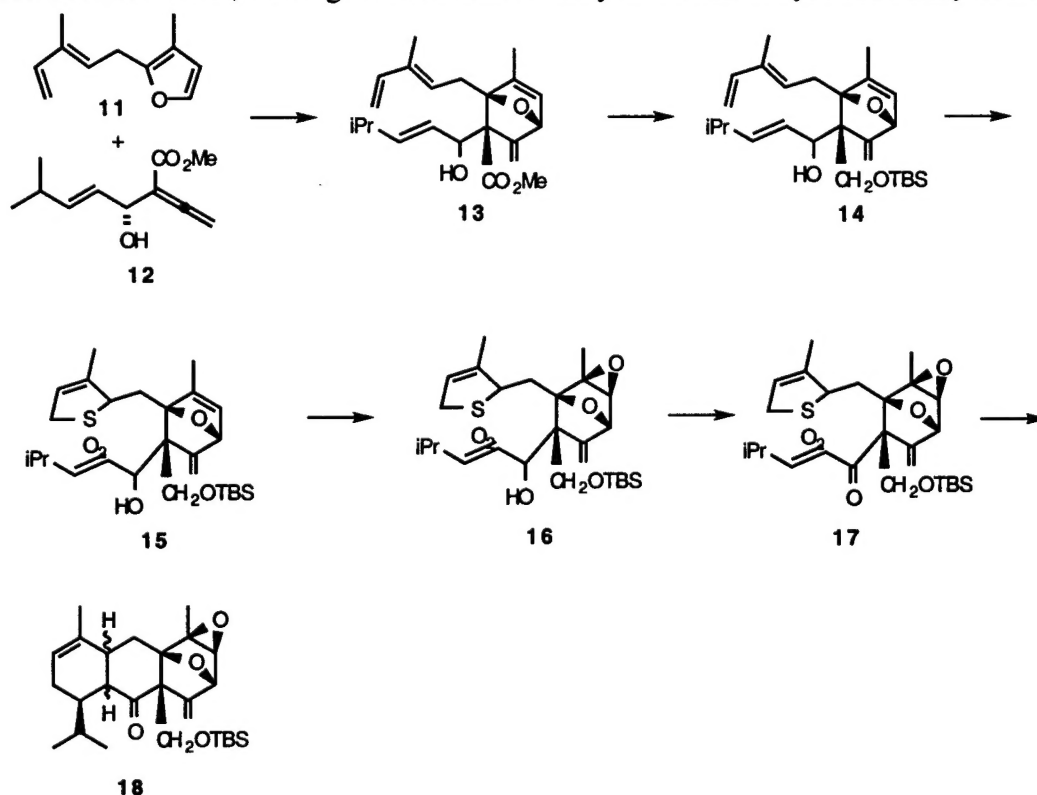


for the same SAR studies that we outlined originally for epothilone. The retrosynthetic analysis for our proposed construction of eleutherobin is outlined in the Scheme above.

Significant progress has been achieved in realizing the proposed scheme. First, we have developed a highly efficient approach to the synthesis of the key bis-diene moiety 11 as outlined below.



Second, we have established the viability of both the inter- and intramolecular cycloaddition reactions outlined in the retrosynthetic scheme. As shown below, the synthesis of the pentacyclic compound 18 (the silyl ether corresponding to the ester 9 in the retrosynthesis) has been achieved, although the stereochemistry of 18 has not yet been fully determined.



As described in the original application, we are continued our modeling studies in an effort to establish a general method for the establishment of the pharmacophore for structurally dissimilar ligands when the structure of the binding site is not known.

Relevance to the Original Hypothesis: Significant progress has been achieved in the efficient synthesis of a highly potent microtubule binding natural product, eleutherobin.

KEY RESEARCH ACCOMPLISHMENTS:

- * A highly efficient synthesis of the bis-diene moiety has been developed
- * Preliminary results indicate that the key Diels-Alder methodology works well and leads to an efficient synthesis of the key intermediate 18 for the fragmentation studies; and
- * Work is underway to develop a general method for the identification of pharmacophores of structurally dissimilar substances using the RigFit program.

REPORTABLE OUTCOMES:

A publication is in preparation describing the synthesis of the bis-diene and the preparation of the pentacyclic intermediate 18.

CONCLUSIONS:

We have established that the proposed retrosynthetic scheme leads to an efficient preparation of the key intermediate for the proposed fragmentation approach to the synthesis of eleutherobin, a potent microtubule binding antimitotic. If the fragmentation reaction works well, this will result in an important improvement in the laboratory synthesis of this scarce natural product, facilitating the preparation of analogs for SAR studies. The ultimate goal of this work is to develop new drugs for prostate cancer based on these taxol-like substances.

APPENDIX:

A current cv for the PI.

CURRICULUM VITAE

NAME: Jeffrey David Winkler

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BIRTH DATE: April 14, 1956

EDUCATION:

Post-doctoral: Columbia University. January 1982-August 1983.
Research Director: Professor Ronald Breslow.

Graduate: Columbia University. September 1977-December 1981.
M.A. 1978, M.Phil., Ph.D. 1981.
Thesis Advisor: Professor Gilbert Stork.

Undergraduate: Harvard College. September 1973-June 1977.
A. B. cum laude in Chemistry, 1977.

PROFESSIONAL EXPERIENCE: Professor, University of Pennsylvania
Department of Chemistry, July 1996-

Founding Member, University of Pennsylvania
Center for Cancer Pharmacology, May 1998-present

Associate Professor, University of Pennsylvania,
Department of Chemistry, July 1990-June 1996
Member, University of Pennsylvania Cancer Center,
July 1993-present

Assistant Professor, University of Chicago,
Department of Chemistry, September 1983-June 1990

AWARDS & HONORS: American Chemical Society Cope Scholar Award, 2000
Parke-Davis Lecturer, Michigan State University, 2000
Chairman, Philadelphia Organic Chemists' Club, 1995
H. Martin Friedmann Lecturer, Rutgers University, 1993
American Cyanamid Young Faculty Award, 1989-1992
NIH-NCI Research Career Development Award, 1988-1993
Alfred P. Sloan Research Fellow, 1987-1989
Merck Foundation Award for Faculty Development, 1985
American Cancer Society Postdoctoral Fellow, 1982-1983

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RESEARCH SUPPORT

ACTIVE

CA 40250-08A2 (Winkler) 2/5/98-12/31/00 20%
National Institutes of Health \$191,555 (direct costs/year)
Strategies for the Synthesis of Antitumor Compounds
This proposal is directed towards the development of new approaches to the construction of the naturally occurring substances manzamine and ingenol.

N-00014-93-1-0836 (Winkler) 10/1/95-9/30/99 5%
Office of Naval Research \$85,513 (direct costs/year)
Binding and Transport of Metal Ions
This proposal is directed towards the development of immobilized and fluorescent systems for the development of metal ion sensors for use in the marine environment.

BCRP-971965 (Winkler) 7/15/98-7/14/01 20%
DOD Breast Cancer Research Program (IDEA) \$69,905 (direct costs/year)
Design and Synthesis of New Breast Cancer Chemotherapeutic Agents
This proposal is directed towards design and synthesis of new breast cancer chemotherapeutic agents based on taxol and epothilone. The synthetic work in this proposal is directed towards the synthesis of bicyclic analogs of epothilone

PRF-AC (33255) (Winkler) 9/01/98-8/31/00 5%
Petroleum Research Fund \$30,000 (direct costs/year)
Novel Chemical Systems Based on Spiropyran Indolines
This proposal is directed towards the development of spiropyran as control mechanisms for the design and synthesis of gating mechanisms for signal transduction, a critical component in the construction of molecular devices.

PC970475 (Winkler) 9/1/98-2/28/01 20%
DOD Prostate Cancer Research Program \$114,960 (direct costs/year)
Design and Synthesis of New Prostate Cancer Chemotherapeutic Agents
This proposal is directed towards design and synthesis of new prostate cancer chemotherapeutic agents based on taxol and epothilone. The synthetic work in the DOD PC grant is directed towards the synthesis of the left- and right-hand halves of an X-ray based bridged bicyclic analog of epothilone

Boehringer Ingelheim 1/1/99-12/31/99 (0%)
Synthesis of α -Methyl- α -Amino Acids \$37,670 (direct costs/year)
This proposal involves support for one postdoctoral on a project that is directed towards a novel approach to the synthesis of amino acids.

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PROFESSIONAL ACTIVITIES

Consultant, Wyeth-Ayerst Pharmaceuticals (1998-)

Associate Editor, *Organic Letters* (1999-)

INVITED LECTURES SINCE 1990:

Merck, Sharp & Dohme (West Point, PA)

Smith, Kline and Beckmann

Invited Lecturer, Symposium on Organic Synthesis, Great Lakes Regional ACS Meeting,

Dekalb, Illinois Invited Lecturer, Molecular Recognition Meeting, Office of Naval

Research, Charleston, S.C

Invited Lecturer, Symposium on Heterocyclic Chemistry, National ACS Meeting,

Washington, D.C

Squibb Institute for Medical Research (Princeton, NJ)

University of Rochester

Squibb Institute for Medical Research (New Brunswick, NJ)

Boehringer-Ingelheim Pharmaceuticals

Brandeis University

University of Delaware

ICI Pharmaceuticals

New York Academy of Sciences

North Jersey ACS Meeting

Invited Lecture, 1992 Meeting of the American Society for Photobiology

Organizer and Lecturer, Symposium on Studies Toward the Total Synthesis of Taxol,

National ACS Meeting, San Francisco, CA. (April 8, 1992)

Dupont Agricultural Products

Burroughs Wellcome

University of Virginia

Sandoz Institute

Sterling Winthrop

Bryn Mawr College

Invited Lecturer, Symposium on Organic Chemistry, Great Lakes Regional ACS Meeting,

Ann Arbor, Michigan

Invited Lecturer, Symposium on Organic Synthesis, Middle Atlantic Regional ACS

Meeting, Baltimore, Maryland

Technion-Israel Institute of Technology

Pfizer Central Research

Sandoz Institute

Hebrew University of Jerusalem

R. W. Johnson

University of Montreal

Plenary Lecturer, Wyeth-Ayerst Fourth Annual Chemical Sciences Symposium

Merck (West Point, PA)

American Cyanamid

Rhone-Poulenc Agricultural

Plenary Lecture, Interamerican Photochemical Society

University of Maryland

R. W. Johnson Pharmaceutical Research

Wyeth-Ayerst

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Sepracor

Boehringer-Ingelheim

Florida State University

Northwestern University

UCLA

University of Minnesota

Parke-Davis

Pfizer

Penn State University

Smith Kline Beecham

Temple University

Amgen

University of Chicago

Dupont Pharmaceuticals

Invited Speaker, Symposium on Solid Support Chemistry, Middle Atlantic Regional ACS Meeting, May 1999

Plenary Lecturer, Symposium on Heterocycles, Canadian Institute of Chemistry, June 1999

Invited Speaker, Gordon Conference on Heterocycles, July 2000

University of Western Ontario

Boehringer-Ingelheim, Montreal

Michigan State University

PUBLICATIONS :

1. L. Blaszcak, J. Winkler, S. O'Kuhn, "A New Synthesis of Olefins from Ketones via Coupling of Lithium Dialkylcuprates with Enol Phosphate Diesters," *Tetrahedron Lett.* **1976**, 4405-4408.
2. G. Stork, C. Shiner, J. Winkler, "Stereochemical Control of the Internal Michael Reaction. A New Construction of trans-Hydrindane Systems," *J. Am. Chem. Soc.* **1982**, *104*, 310-312.
3. G. Stork, J. Winkler, C. Shiner, "Stereochemical Control of Intramolecular Conjugate Addition. A Short, Highly Stereoselective Synthesis of Adrenosterone," *J. Am. Chem. Soc.* **1982**, *104*, 3767-3768.
4. G. Stork, J. Winkler, N. Saccomano, "Stereochemical Control in the Construction of Vicinally Substituted Cyclopentanes and Cyclohexanes. Intramolecular Conjugate Addition of β -Ketoester Anions," *Tetrahedron Lett.* **1983**, 465-468.
5. J. Winkler, E. Coutouli-Argyropoulou, R. Leppkes, R. Breslow, "An Artificial Transaminase Carrying A Synthetic Macrocyclic Binding Group," *J. Am. Chem. Soc.* **1983**, *105*, 7198-7199.
6. W. Weiner, J. Winkler, S. Zimmerman, R. Breslow, "Mimics of Tryptophan Synthetase and of Biochemical Dehydroalanine Formation," *J. Am. Chem. Soc.* **1985**, *107*, 4093-4094.

7. R. Breslow, A. W. Czarnik, M. Lauer, H. Leppkes, J. Winkler, S. Zimmerman, "Mimics of Transaminase Enzymes," *J. Am. Chem. Soc.* **1986**, *108*, 1969-1979.
8. J. Winkler, V. Sridar, "Stereochemical Control of Transannular Radical Cyclizations. A New Approach to the Synthesis of Linearly Fused Cyclopentanoids," *J. Am. Chem. Soc.* **1986**, *108*, 1708-1709.
9. J. Winkler, J. Hey, P. Williard, "Inside-Outside Stereoisomerism: A Synthesis of *trans*-Bicyclo[5.3.1]undecan-11-one," *J. Am. Chem. Soc.* **1986**, *108*, 6425-6427.
10. J. Winkler, P. Hershberger, J. Springer, "A Stereoselective Synthesis of the Azaspirodecane Ring System of (-)-Histriocotoxin from (+)-Glutamic Acid," *Tetrahedron Lett.* **1986**, 5177-5180.
11. J. Winkler, J. Hey, S. Darling, "Studies Directed Towards the Synthesis of the Taxane Diterpenes: A Remarkable Rearrangement," *Tetrahedron Lett.* **1986**, 5959-5962.
12. J. Winkler, J. Hey, F. Hannon, P. Williard, "Intramolecular Photoaddition of Dioxolenones. An Efficient Method for the Synthesis of Medium-Sized Rings," *Heterocycles* **1987**, *25*, 55-60.
13. J. Winkler, K. Deshayes, "Photodynamic Macrocycles," *J. Am. Chem. Soc.* **1987**, *109*, 2190-2191.
14. J. Winkler, K. Henegar, P. Williard, "Inside-Outside Stereoisomerism II. Synthesis of the Carbocyclic Ring System of the Ingenane Diterpenes *via* the Intramolecular Dioxolenone Photocycloaddition," *J. Am. Chem. Soc.* **1987**, *109*, 2850-2851.
15. K. Henegar, J. Winkler, "A New Method for the Synthesis of Dioxolenones *via* the Carboxylation of Ketone Enolates with Anisyl Cyanoformate," *Tetrahedron Lett.* **1987**, 1051-1054.
16. J. Winkler, C. Muller, R. Scott, "A New Method for the Formation of Nitrogen-Containing Ring Systems *via* the Intramolecular Photocycloaddition of Vinylogous Amides. A Synthesis of Mesembrine," *J. Am. Chem. Soc.* **1988**, *110*, 4831-4832.
17. J. Winkler, J. Hey, P. Williard, "Inside-Outside Stereoisomerism III. The Synthesis of *trans*-Bicyclo[4.3.1]Decan-10-one," *Tetrahedron Lett.* **1988**, 4691-4694.
18. J. Winkler, V. Sridar, "Eight-Membered Ring Templates for Stereoselective Radical Cyclizations," *Tetrahedron Lett.* **1988**, 6219-6222.
19. J. Winkler, K. Deshayes, B. Shao, "Photodynamic Systems for Metal Ion Transport," *J. Am. Chem. Soc.* **1989**, *111*, 769-770.
20. J. Winkler, P. Hershberger, "A Stereoselective Synthesis of (-)-Perhydrohistriocotoxin," *J. Am. Chem. Soc.* **1989**, *111*, 4852-4856.

21. J. Winkler, V. Sridar, L. Rubo, J. Hey, N. Haddad, "Inside-Outside Stereoisomerism IV. An Unusual Rearrangement of the trans-Bicyclo[5.3.1]Undecan-11-yl Radical," *J. Org. Chem.* **1989**, *54*, 3004-3006.
22. J. Winkler, C. Lee, L. Rubo, C. Muller, P. J. Squattrito, "Stereoselective Synthesis of the Tricyclic Skeleton of the Taxane Diterpenes. The First C-Silylation of a Ketone Enolate," *J. Org. Chem.* **1989**, *54*, 4491-4493.
23. J. Winkler, V. Sridar, M. Siegel, "Ten-Membered Ring Templates for Stereoselective Radical Cyclizations," *Tetrahedron Lett.* **1989**, 4943-4946.
24. J. Winkler, C. Muller, J. Hey, R. Ogilvie, N. Haddad, P. Squattrito, P. Williard, "The Effect of Chromophore Transposition on the Stereochemical Outcome of the Intramolecular Dioxenone Photocycloaddition Reaction," *Tetrahedron Lett.* **1989**, 5211-5214.
25. J. Winkler, N. Haddad, R. Ogilvie, "Intramolecular Photocycloaddition and Retro-Mannich Fragmentation of Tertiary Vinylogous Amides," *Tetrahedron Lett.* **1989**, 5703-5704.
26. J. Winkler, M. Finck-Estes, "Carbon-Carbon Bond Formation Under Aqueous Reaction Conditions Using Sulfonium and Selenonium Salt Electrophiles," *Tetrahedron Lett.* **1989**, 7293-7296.
27. J. Winkler, R. Scott, P. Williard, "Asymmetric Induction in the Vinylogous Amide Photocycloaddition. A Formal Synthesis of Vindorosine," *J. Am. Chem. Soc.* **1990**, *112*, 8971-8975.
28. J. Winkler, B. Hong, "Inside-Outside Stereoisomerism V. Synthesis and Reactivity of Bicyclo[n.3.1]alkanones with trans Intrabridgehead Stereochemistry," *J. Am. Chem. Soc.* **1991**, *113*, 8839-8846.
29. J. Winkler, E. Gretler, "Stereoselective Cyclopropanation of Homoallylic Alcohols. Formal Attachment of a Cyclopropane to a Preexisting Ring," *Tetrahedron Lett.* **1991**, 5733-36.
30. J. Winkler and D. Subrahmanyam, "Studies Directed Towards the Synthesis of Taxol: Preparation of C-13 Oxygenated Taxane Congeners," *Tetrahedron* **1992**, *48*, 7049-7056.
31. J. Winkler, E. Gretler, P. Williard, "Studies Directed Towards the Synthesis of the Ingenane Diterpenes. An Unexpected Synthesis of trans-Bicyclo[5.3.0]Decanes," *J. Org. Chem.* **1993**, *58*, 1973-1975.
32. J. Winkler, B. Hong, A. Bahador, M. Kazanietz, P. Blumberg, "Synthesis of Ingenol Analogs with Affinity for Protein Kinase C," *Bioorg. Med. Chem. Lett.* **1993**, *3*, 577-580.
33. J. Winkler, B. Shao, "On the Stereoselectivity of the Intramolecular Dioxenone Photocycloaddition Reaction," *Tetrahedron Lett.* **1993**, 3355-3358.

34. J. Winkler, M. Siegel, and J. Stelmach, "A Highly Stereoselective Approach to the Synthesis of the Manzamine Alkaloids via the Intramolecular Vinylogous Amide Photocycloaddition," *Tetrahedron Lett.* **1993**, 6509-6512.
35. J. Winkler, K. Deshayes and Bin Shao, "Photochemical Binding, Release and Transport of Metal Ions." In *Bioorganic Photochemistry*, **1993**, Volume II, H. Morrison, Ed., Wiley, New York, Chapter 3, pp. 169-196.
36. J. Winkler, M. Siegel, "A Novel Photochemical Synthesis of Pyrroles from β -Ketovinylogous Amides," *Tetrahedron Lett.* **1993**, 7697-7700.
37. M. Siegel and J. Winkler, "Photochemistry of Enamines and Enaminones" In *The Chemistry of Enamines*, **1994**, S. Patai and Z. Rappaport, Eds., Wiley, New York, 637-679.
38. J. Winkler, K. Henegar, B. Hong and P. Williard, "Inside-Outside Stereoisomerism. 6. Synthesis of *trans*-Bicyclo[4.4.1]Undecan-11-one and the First Stereoselective Construction of the Ingenane Nucleus," *J. Am. Chem. Soc.* **1994**, *116*, 4183-4188.
39. J. Winkler, B. Hong, "*Trans*-Bicyclo-[5.3.1]undecan-11-one," in *Photochemical Key Steps in Organic Synthesis 1994*, J. Mattay and A. Griesbeck, Eds., VCH, Weinheim, 109-111.
40. K. Davis, T. Berrodin, T., J. Stelmach, J. Winkler, M. Lazar, "Endogenous RXRs can function as hormone receptors in pituitary cells," *Molecular and Cell Biology* **1994**, *14*, 7105-7110.
41. J. Winkler, S. Kim, K. Condroski, A. Asensio, K. N. Houk, "Stereoselective Synthesis of Polycyclic Ring Systems via the Tandem Diels-Alder Reaction," *J. Org. Chem.* **1994**, *59*, 6879-6881.
42. J. Winkler, B. Hong, "Transannular Radical Reactions in Bicycloalkanes with 'Inside-Outside' Stereochemistry. An Unusual Bridgehead Hydroxylation," *Tetrahedron Lett.* **1995**, 683-686.
43. J. Winkler, H. Kim, S. Kim, "A Highly Efficient Synthesis of Taxanes via the Tandem Diels-Alder Reaction," *Tetrahedron Lett.* **1995**, 687-691.
44. J. Winkler, B. Hong, A. Bahador, M. Kazanietz, P. Blumberg, "Methodology for the Synthesis of 3-Oxygenated Ingenanes--The First Ingenol Analogs with High Affinity for Protein Kinase C," *J. Org. Chem.* **1995**, *60*, 1381-1390.
45. J. Winkler, S. Bhattacharya, F. Liotta, R. Batey, G. Heffernan, D. Cladingboel, R. Kelly, "Stereoselective Synthesis of A Synthon for the A-Ring of Taxol from R-(+)-Verbenone," *Tetrahedron Lett.* **1995**, 2211-2215.
46. J. Winkler, B. Hong, S. Kim, N. Lewin, P. Blumberg, "On the Protein Kinase C Pharmacophore: Synthesis and Biological Activity of 4-Hydroxylated Analogs of Ingenol," *Synlett* **1995**, 533-535.

47. H. Li, S. Narasimhulu, L. Havran, J. Winkler, T. Poulos, "Crystal Structure of Cytochrome P-450 Complexed with Its Catalytic Product, 5-Exo-Hydroxycamphor," *J. Am. Chem. Soc.* **1995**, *117*, 6297-6299.
48. J. Winkler, C. Mazur, and F. Liotta, "[2+2]Photocycloaddition-Fragmentation Strategies for the Synthesis of Natural and Unnatural Products," *Chem. Rev.* **1995**, *95*, 2003-2020.
49. J. Winkler, "The Tandem Diels-Alder Reaction," *Chem. Rev.* **1996**, *96*, 167-176.
50. J. Winkler, J. Stelmach, J. Axten, "Two Highly Efficient Syntheses of Scalemic Azocines," *Tetrahedron Lett.* **1996**, 4317-4320.
51. J. Winkler, S. Bhattacharya, R. Batey, "Synthesis of a Taxinine Congener via the Intramolecular Diels-Alder Cycloaddition," *Tetrahedron Lett.* **1996**, 8069-8072.
52. J. Winkler, J. Holland, D. Peters, "Synthesis of Cyclopropyl Taxane Analogs via Sequential Diels-Alder Reactions," *J. Org. Chem.* **1996**, *61*, 9074-9075.
53. J. Winkler and P. Axelsen, "A Model for the Taxol/Epothilone Pharmacophore," *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2963-2966.
54. J. Winkler, H. Kim, S. Kim, K. Ando, K. Houk, "Stereoselective Synthesis of the Taxane Ring System via the Tandem Diels-Alder Cycloaddition," *J. Org. Chem.* **1997**, *62*, 2957-2962.
55. J. Winkler, J. Stelmach, M. Siegel, N. Haddad, J. Axten, W. Dailey, "An Approach to the Synthesis of the Manzamine Alkaloids via the Vinylogous Amide Photocycloaddition-retro-Mannich Fragmentation-Mannich Closure Cascade," *Isr. J. Chem.* **1997**, *37*, 47-67.
56. S. Kim, J. Winkler, "Approaches to the Synthesis of Ingenol," *Chem. Soc. Rev.* **1997**, *26*, 387-400.
57. J. Winkler, E. Doherty, "Control of Relative Stereochemistry of Quaternary Carbon Centers via the Intramolecular Dioxenone Photocycloaddition: An Approach to the Synthesis of Saudin," *Tetrahedron Lett.* **1998**, 2253-2256.
58. J. Winkler, C. Bowen, V. Michelet, "Photodynamic Fluorescent Metal Ion Sensors with ppb Sensitivity," *J. Am. Chem. Soc.* **1998**, *120*, 3237-3242.
59. S. Narasimhulu, L. Havran, P. Axelsen, J. Winkler, "Interactions of Substrate and Product with Cytochrome P450," *Arch. Biochem. Biophys.* **1998**, *353*, 228-238.
60. J. Winkler, J. Axten, H. Hammach, Y. Kwak, M. Lucero, K. Houk, "Stereoselective Synthesis of the Tetracyclic Core of the Manzamine Alkaloids via the Vinylogous Amide Photocycloaddition Cascade: A Remarkable Effect of Azocine Unsaturation on the Stereochemical Outcome of the Photocycloaddition Reaction," *Tetrahedron* **1998**, *54*, 7045-7056.

61. J. Winkler, W. McCoull, "Diels-Alder Reaction on Solid Supports Using Polymer-Bound Oxazolidinones," *Tetrahedron Lett.* **1998**, 4935-4936.
62. J. Winkler, J. Axten, "The First Total Syntheses of Ircinol A, Ircinal A, and Manzamines A and D," *J. Am. Chem. Soc.* **1998**, *120*, 6425-6426.
63. J. Winkler, Y. Kwak, "An Approach to Controlled Oligomerization via Iterative Diels-Alder Cycloadditions on Solid Supports," *J. Org. Chem.* **1998**, *63*, 8634-8635.
64. J. Axten, L. Krim, H. Kung, J. Winkler, "An Improved Synthesis of *dl*-threo-Methylphenidate. Preparation and Biological Evaluation of Novel Analogs," *J. Org. Chem.* **1998**, *63*, 9628-9629.
65. J. Winkler, S. Kim, S. Harrison, N. Lewin, P. Blumberg, "Synthesis and Biological Evaluation of Highly Functionalized Analogs of Ingenol: The Importance of Hydrophobic Effects on Binding to Protein Kinase C," *J. Am. Chem. Soc.*, **1999**, *121*, 296-300.
66. G. Collins, L. Choi, K. Ewing, V. Michelet, C. Bowen, and J. Winkler, "Photoinduced Switching of Metal Complexation by Quinolinospiropyranindolines in Polar Solvents," *J. Chem. Soc., Chem. Commun.* **1999**, 321-322.
67. J. Winkler, J. Holland, J. Kaspavec, and P. Axelsen, "Synthesis and Biological Evaluation of Constrained Epothilone Analogs: The Efficient Synthesis of Eleven-Membered Rings by Olefin Metathesis," *Tetrahedron* (invited contribution to Symposium-in-Print on Olefin Metathesis in Synthesis) **1999**, *55*, 8199-8214.
68. J. Axten, R. Ivy, L. Krim, J. Winkler, "An Enantioselective Synthesis of d-threo-Methylphenidate," *J. Am. Chem. Soc.* **1999**, *121*, 6511-6512.
69. J. Winkler, E. Doherty, "The First Total Synthesis of (\pm)-Saudin," *J. Am. Chem. Soc.* **1999**, *121*, 7425-7426.